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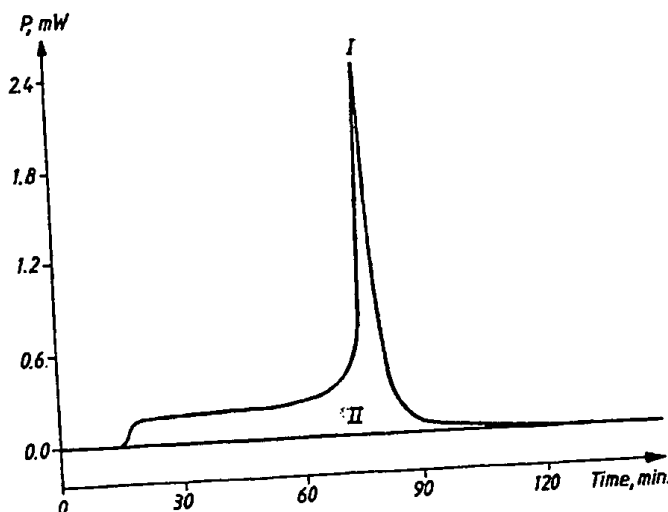
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(57) Abstract

The present invention relates to a process for providing a stable crystalline form to a fine-grained substance or a substance mixture, which can be produced, stored and used while maintaining the aerodynamic properties required for inhalation of such a substance or a substance mixture, by a) in case of a substance mixture, preparing a homogeneous mixture of the substances; b) micronizing, direct precipitating or diminishing by any conventional method the substance or substance mixture into a particle size required for inhalation, the particle size being less than 10 μm ; c) optionally preparing a homogeneous mixture of the desired substances when each substance has been introduced from stage b) as separate fine-grained particles; d) conditioning said substance or substance mixture by treatment with a water containing vapour phase in a controlled fashion; and e) drying.

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Process for conditioning substances

5

Field of the invention

The present invention relates to a process for providing a fine-grained substance or substance
10 mixture, which can be produced, stored and used while maintaining the aerodynamic properties required for inhalation of such a substance or substance mixture and which have improved physicochemical properties in the dry state, thereby facilitating the technical handling
15 and significantly increase the medical value of the formulation used.

Background of the invention

20 There are presently several effective drugs available for the treatment of patients with asthma or other respiratory disorders. It has been recognized that these drugs should be given by the inhaled route whenever possible. The ideal delivery system for
25 inhalable drugs would be a user- and environment-friendly multidose inhaler giving accurate doses of a stable formulation with good aerodynamic behaviour of the particles.

30 During the past few years, there have been frequent demonstrations of the fact that the appropriate selection of the most suitable crystalline modification significantly can influence the clinical results of a given chemical substance. The chemical and physical
35 stability of a solid in a particular dosage form can be improved by presenting the substance(s) in the appropriate crystal form. The solid state phase

transformation of the substance in a dosage form can dramatically alter the pharmaceutical properties of the formulation. The solid state phase of the administered substance(s) can influence such important factors as
5 bioavailability and physicochemical stability (specific surface area, particle size etc). Chemical stability in solid state and hygroscopicity are often closely related to the crystallinity.

10 Solid state transformations may occur during mechanical processing e.g. micronization. In a micronization process of solids, disruption or activation of the crystalline structure often leads to varying degrees of
15 disorder through the formation of defects or amorphous regions. Such regions are often more sensitive to external effects e.g. moisture. It is necessary to establish the conditions whereby different forms of a substance might be converted to a single stable form thus eliminating differences in solid state properties
20 and subsequent different physicochemical and pharmaceutical properties.

The increasing production and use of fine powders in the pharmaceutical industry has highlighted the need of
25 reliable methods for assessing their physicochemical and technical handling. Mixing of cohesive powders will be influenced by the interparticulate forces between particles of the same species and also between particles of different species. Since fine powders
30 agglomerate, the mixture will often be inhomogeneous, particularly the minor component will show a skewed distribution. One reason could be that the agglomerates of the minor component is not completely dispersed into their component particles; see further Chem. Eng.
35 (1973), 12-19. Cohesive powders are thus very difficult to mix to a homogenous mixture in an accurate way, especially when one component is present only as a

small fraction.

Substances will often be obtained in an amorphous state or a metastable crystalline form when spray drying, freeze drying, rapid solvent quenching or when using controlled precipitation, where both crystalline and amorphous forms can be prepared. The use of an amorphous form or metastable crystalline form is often limited due to its thermodynamic instability. It is therefore a desire to convert the amorphous form or the metastable crystalline form to the more stable crystalline state. For crystalline substances, a diminution operation step will give amorphous regions of the particle making the particle more sensitive to moisture and chemical degradation. The present invention deals with such physical changes, or more importantly, to anticipate them and the means by which these solid state phenomena can be handled.

The rearrangement or conditioning of a water-soluble substance, amorphous or partly amorphous, using a solvent like ethanol, acetone or the like has been described in Eur. Pat. Appl. EP 508 969 where single compounds have been applied. However, that method is not applicable for some substances containing crystal water, since organic solvents will eliminate the water thereby changing the properties of the substance considerably. It has been understood that water-soluble substances could not be conditioned by water while keeping the particle distribution of a fine-grained substance intact.

References:

- Amorphous-to-Crystalline Transformation of Sucrose,
Phar. Res., 7(12), 1278 (1990) by J.T. Carstensen and K. Van Scoik.
Effect of Surface Characteristics of Theophylline

Anhydrate Powder on Hygroscopic Stability, J. Pharm. Pharmacol. 42, 606 (1990) by M. Otsuka et al.

Process for conditioning of water-soluble substances, Eur. Pat. Appl. 508969 by J. Trofast et al.

- 5 The molecular basis of moisture effect on the physical and chemical stability of drugs in the solid state, Int. J. Pharm. 62(1990), 87-95 by C. Ahlneck and G. Zografli.

10 Brief description of the invention

The object of the invention is to provide a process for a fine-grained substance or substance mixture, which can be produced, stored and used while maintaining the aerodynamic properties required for inhalation of such a substance or substance mixture, whereby conditioning the mixture in a controlled process, thereby facilitating the technical handling and significantly increase the medical value of the formulation used.

20

Detailed description of the invention

The object of the present invention is to provide a reliable process for providing a stable crystalline form to a fine-grained substance or a substance mixture, which can be produced, stored and used while maintaining the aerodynamic properties required for inhalation of such a substance or a substance mixture. The process according to the present invention comprises the following steps:

30

a) in case of a substance mixture, preparing a homogenous mixture of the substances;

35

b) micronizing, direct precipitating or diminishing by any conventional method the substance or substance mixture into a particle

size required for inhalation, the particle size being less than $10\mu\text{m}$;

5 c) optionally preparing a homogenous mixture of the desired substances when each substance has been introduced from stage b) as separate fine-grained particles;

10 d) conditioning said substance or substance mixture by treatment with a water containing vapour phase in a controlled fashion; and

e) drying.

15 The conditioning step is carried out by treatment with a water containing vapour phase. Said water containing vapour phase is a water vapour phase with or without any organic solvent vapour present.

20 The conditioning step is carried out at a temperature/relative humidity combination, which suppresses the glass temperature of substances involved below the process temperature. The glass temperature (T_g) is the temperature at which the mobility of an
25 amorphous material undergoes changes from an immobile glassy state to mobile rubbery state (phase transition).

The conditioning is generally carried out at a
30 temperature between 0 and 100°C , preferably between 10 and 50°C . Of practical reasons the conditioning is often performed at ambient temperature. The relative humidity (RH) at which the conditioning is carried out is chosen so that the phase transition occurs, mainly
35 above 35% RH, preferably above 50% RH, and most preferably above 75% RH. The time used is considerably influenced by the batch size, relative humidity and

packing etc and may be from minutes to days.

The final formulation may also include different additives, e.g. a substance which enhances the
5 absorption of a pharmacologically active drug in the lung. The enhancers used can be any of a number of compounds which act to enhance absorption through the layer of epithelial cell lining the alveoli of the lung and into the adjacent pulmonary vasculature. Among the
10 substances with known absorption-enhancing properties are surfactants, such as alkali salts of fatty acids, sodium tauro-dihydrofusidate, lecithins, sodium glycocholate, sodium taurocholate, octylglucopyranoside and the like.

15 Other additives in the formulation may be carriers, diluents, antioxidants, buffer salts and the like, all of which will be treated according to the process of the present invention.

20 The accuracy and reproducibility of doses are often not sufficient when using very small doses in an inhalation device. Therefore very potent drugs may be diluted with a carrier in order to get an amount of powder
25 sufficient to obtain a reliable and reproducible dose. Such a carrier may be carbohydrates like lactose, glucose, fructose, galactose, trehalose, sucrose, maltose, raffinose, maltitol, melezitose, starch, xylitol, mannitol, myoinositol, and the like and its
30 hydrates, preferably lactose and mannitol, and amino acids such as alanine, betaine and the like.

Coarser particles having a size above 10 μm may also be
35 conditioned using the process according to the present invention.

The present invention may be applied to for example the following pharmacologically active substances:

5 Formoterol (e.g. as fumarate) and salmeterol (e.g. as xinafoate) are highly selective long-acting β_2 -adrenergic agonists having bronchospasmodolytic effect and are effective in the treatment of reversible obstructive lung ailments of various genesis, particularly asthmatic conditions. Salbutamol (e.g. as
10 sulphate), bambuterol (e.g. as hydrochloride), terbutaline (e.g. as sulphate), fenoterol (e.g. as hydrobromide), clenbuterol (e.g. as hydrochloride), procaterol (e.g. as hydrochloride), bitolterol (e.g. as mesylate) and broxaterol are highly selective β_2 -
15 adrenergic agonists and ipratropium bromide is an anticholinergic bronchodilator. Examples on antiinflammatory glucocorticoids are budesonide, (22R)-6 α ,9 α -difluoro-11 β ,21-dihydroxy-16 α ,17 α -propylmethylenedioxy-4-pregnen-3,20-dione, fluticasone
20 (e.g. as propionate ester), beclomethasone (e.g. as dipropionate ester), tipredane, momethasone and the like. Several of the compounds could be in the form of pharmacologically acceptable esters, salts, solvates, such as hydrates, or solvates of such esters or salts,
25 if any.

The preferred substances to which the invention is to be applied are terbutaline sulphate, salbutamol sulphate, fenoterol hydrobromide, ipratropium bromide,
30 bambuterol hydrochloride, formoterol fumarate and salmeterol xinafoate, and their solvates, especially their hydrates.

The most preferred substance mixture to which the
35 invention is to be applied is formoterol (as formoterol fumarate dihydrate)/lactose (monohydrate), although the same principle may be applied to combinations such as

salbutamol (as salbutamol sulphate)/lactose,
terbutaline (as terbutaline sulphate)/lactose,
ipratropium bromide/lactose, budesonide/lactose, (22R)-
6 α ,9 α -difluoro-11 β ,21-dihydroxy-16 α ,17 α -
5 propylmethylenedioxy-4-pregnen-3,20-dione/mannitol,
(22R)-6 α ,9 α -difluoro-11 β ,21-dihydroxy-16 α ,17 α -
propylmethylenedioxy-4-pregnen-3,20-dione/myoinositol
and (22R)-6 α ,9 α -difluoro-11 β ,21-dihydroxy-16 α ,17 α -
propylmethylenedioxy-4-pregnen-3,20-dione/lactose. When
10 one of the components is rather insoluble in water, it
is possible to use an organic solvent as a conditioning
agent for one compound and water vapour as a
conditioning agent for the other one in the
conditioning step. In that case the conditioning may be
15 carried out in a two step procedure wherein the first
step is conditioning with an organic solvent followed
by conditioning by water vapour in a second step; or
vice versa.

20 The rearrangement or conditioning of the substance or
substance mixture, amorphous or partly amorphous,
involve treatment of the substance(s) with a water
containing vapour phase in a controlled fashion. This
conditioning step is to be performed in a defined
25 environment with controlled and adjustable humidity or
a column using inert gas and/or organic solvent vapour
containing the required amount of water vapour. The
packing of the substance or substance mixture affects
the time needed as well as the result of the
30 conditioning. The tendency of caking is affecting the
number and size of particles. In case of a substance
mixture, it is usually an advantage to mix the
substances before the micronizing step in order to
ensure a homogenous mixture when using small ratios
35 between the drug substance and the additive.

With the present invention it is possible to condition two or more substances in the same process while the particle distribution is maintained and this is from a technical standpoint a great advantage.

5

The ratio between the substances in a substance mixture is between 1:1 and 1:1000, preferably between 1:1 and 1:500, and most preferred between 1:1 and 1:200 in the case where one substance is a pharmacologically active substance and the other one is an additive.

10

The particle size of the fine-grained substances should be identical before and after the conditioning step as measured by different instruments like Malvern Master Sizer, Coulter Counter or a microscope.

15

It is also of utmost importance that the particles obtained are well-defined in size and distribution as well as have small batch to batch variations in order to obtain agglomerates that will completely disintegrate into its primary particles in the inhaler used.

20

It is an object of the present invention to provide a reliable process, where the drug formulation of a single drug substance or a combination of a drug substance/additive, preferably formoterol fumarate dihydrate/lactose can be conveniently and reproducibly prepared.

25

30

For some material such as formoterol/lactose, where the T_g (the glass transition temperature, the temperature at which the mobility of an amorphous substance undergoes changes from an immobile glassy state to mobile rubbery state) or water sensitivity is markedly different for the drug substance and the additive, the process can be performed in two subsequent steps, i.e.

35

conditioning of one substance at one temperature/RH combination followed by conditioning at a higher temperature/RH for a second substance.

- 5 The mixing step is preferably performed before the micronization step in order to ensure the content uniformity or in a single step using a vibratory ball mill as reported by I. Krycer and J.A. Hersey in Int. J. Pharm. 6, 119-129 (1980). It is also possible to mix
10 the substances after micronization or after each substance has been conditioned.

- 15 In some instances it has been possible to use infrared spectroscopy in order to study the conversion of an amorphous form or a partly crystalline form into a stable crystalline form. Other methods available include BET gas adsorption, X-ray powder diffraction, isothermal microcalorimetry and differential scanning calorimetry (DSC). We have found that BET gas
20 adsorption and isothermal microcalorimetry being the best methods for distinguishing the different forms of the tested compounds.

- 25 When a substance or substance mixture is agglomerated and used as such, a drop of about 70-80% of the respirable particles is found when exposed to high humidity. It has astonishingly been found that a drop of only about 25-30% occurs when a substance or substance mixture has been conditioned (at 50% RH for formoterol fumarate dihydrate/lactose mixture) before
30 agglomeration and exposed to high humidity. After further conditioning at 75% RH a drop of only 5-10% of the respirable particles will occur. There is no difference in particle distribution as measured by a
35 Malver instrument before and after conditioning at 75% RH. If the conditioning is performed with the agglomerated product the particle distribution is

considerable worse and the formulation useless in an inhalation device.

Experimental procedure

5

The invention relates to the following procedure:

1. Mixing the drug substance with the additive in a defined ratio.

10

2. Micronizing the mixture.

3. Conditioning at a temperature/relative humidity combination, which suppresses the glass temperature of substances involved below the process temperature. The glass temperature (T_g) is the temperature at which the mobility of an amorphous material undergoes changes from an immobile glassy state to mobile rubbery state.

20 4. Drying with dry nitrogen or air, or in vacuum.

EXAMPLES

The invention is further illustrated but not limited by the following examples performed according to the described experimental procedure. Several batches of each substance or substance mixture have been measured. The data represents a comparison of the heat (J/g) given off by non-conditioned and conditioned substances when subjected to a water containing vapour phase. The experiments are performed by using a Thermal Activity Monitor 2277 (Thermometrics AB, Sweden).

30

Example 1

Salbutamol sulphate (25%)/lactose (75%)

35	Conditioned at relative humidity (RH)	50-60 % RH
	Non-conditioned substance (J/g)	5-8
	Conditioned substance (J/g)	<0.5

Example 2Ipratropium bromide (6%)/lactose (94%)

	Conditioned at relative humidity (RH)	50-60 % RH
5	Non-conditioned substance (J/g)	6-8
	Conditioned substance (J/g)	<0.5

Example 3Formoterol fumarate dihydrate

10	Conditioned at relative humidity (RH)	75 % RH
	Non-conditioned substance (J/g)	6
	Conditioned substance (J/g)	<0.5

15 Example 4Lactose (see Figure 1)

	Conditioned at relative humidity (RH)	50 % RH
	Non-conditioned substance (J/g)	10-14
	Conditioned substance (J/g)	<0.5

20

Example 5Melezitose

	Conditioned at relative humidity (RH)	50 % RH
25	Non-conditioned substance (J/g)	12
	Conditioned substance (J/g)	<0.5

Example 6Formoterol fumarate dihydrate (2%)/lactose (98%)

30	Conditioned at relative humidity (RH)	50 % RH
	Non-conditioned substance (J/g)	10-14
	Conditioned substance (J/g)	<0.5

35 During a recrystallization a large amount of heat is evolved, and by monitoring the calorimetric signal the sample is checked for any amorphous content. Figure 1 shows micronised lactose before (I) and after (II)

conditioning. Thus, a complete crystallinity has been obtained during the conditioning according to the invention.

CLAIMS

- 5 1. A process for providing a stable crystalline form
to a fine-grained substance or a substance mixture,
which can be produced, stored and used while main-
taining the aerodynamic properties required for in-
halation of such a substance or a substance mixture,
10 c h a r a c t e r i z e d i n
- a) in case of a substance mixture, preparing a
homogenous mixture of the substances;
- 15 b) micronizing, direct precipitating or
diminishing by any conventional method the
substance or substance mixture into a particle
size required for inhalation, the particle
size being less than 10 μ m;
- 20 c) optionally preparing a homogenous mixture
of the desired substances when each substance
has been introduced from stage b) as separate
fine-grained particles;
- 25 d) conditioning said substance or substance
mixture by treatment with a water containing
vapour phase in a controlled fashion; and
- 30 e) drying.
2. A process according to claim 1 c h a r a c -
t e r i z e d i n that the conditioning, in the case of
a substances mixture, may be performed in a one step
35 procedure or a multistep procedure using different
relative humidity/temperature combinations.

3. A process according to claim 1
c h a r a c t e r i z e d in that the substance or
substance mixture is a drug formulation of a single
drug substance or a combination of a drug
5 substance/additive.

4. A process according to claim 1
c h a r a c t e r i z e d that said substance or at
least one of the substances of said substance mixture
10 is selected from formoterol, salmeterol, salbutamol,
bambuterol, terbutaline, fenoterol, clenbuterol,
procaterol, bitolterol, broxaterol, ipratropium
bromide, budesonide, (22R)-6 α ,9 α -difluoro-11 β ,21-
dihydroxy-16 α ,17 α -propylmethylenedioxy-4-pregnen-3,20-
15 dione, fluticasone, beclomethasone, tipredane,
momethasone, and pharmacologically acceptable esters,
salts, solvates, such as hydrates, and solvates of such
esters or salts, if any.

20 5. A process according to claim 1
c h a r a c t e r i z e d in that said substance or at
least one of the substances of said substance mixture
is selected from formoterol fumarate, salmeterol
xinafoate, salbutamol sulphate, bambuterol
25 hydrochloride, terbutaline sulphate, fenoterol
hydrobromide, clenbuterol hydrochloride, procaterol
hydrochloride, bitolterol mesylate, fluticasone
propionate, beclomethasone dipropionate and solvates,
such as hydrates thereof, if any.

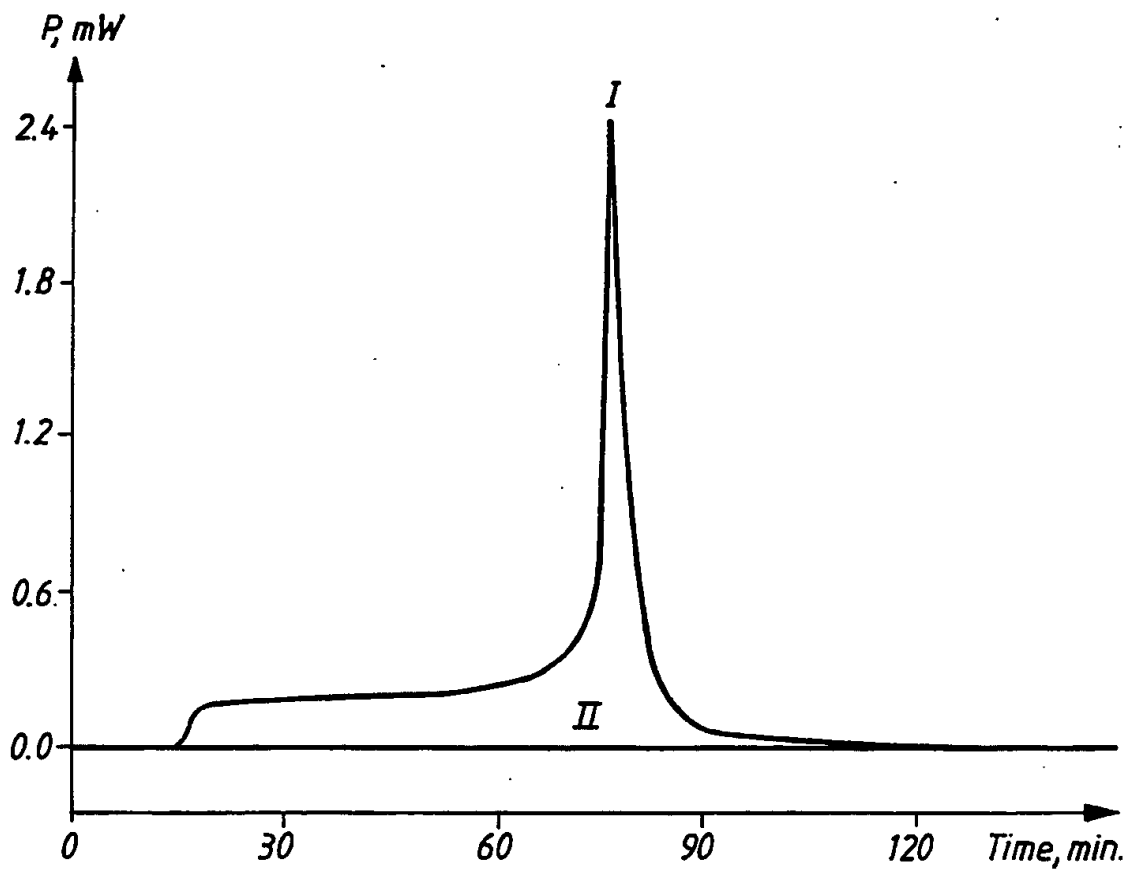
30 6. A process according to claim 3
c h a r a c t e r i z e d that the additive is a
carrier selected from lactose, glucose, fructose,
galactose, trehalose, sucrose, maltose, raffinose,
35 maltitol, melezitose, starch, xylitol, mannitol,
myoinositol, and the like, and its hydrates, preferably
lactose and mannitol, and amino acids such as alanine,

betaine and the like.

7. A process according to claim 3
c h a r a c t e r i z e d that the additive is an
5 enhancer selected from surfactants, such as alkali
salts of fatty acids, sodium tauro-dihydrofusidate,
lecithins, sodium glycocholate, sodium taurocholate,
octylglucopyranoside and the like, or an antioxidant or
a buffer salt.
- 10 8. A process according to claim 1
c h a r a c t e r i z e d in that said substance
mixture is selected from formoterol/lactose,
salbutamol/lactose, terbutaline/lactose, ipratropium
15 bromide/lactose, budesonide/lactose, (22R)-6 α ,9 α -
difluoro-11 β ,21-dihydroxy-16 α ,17 α -propylmethylenedioxy-
4-pregnen-3,20-dione/mannitol, (22R)-6 α ,9 α -difluoro-
11 β ,21-dihydroxy-16 α ,17 α -propylmethylenedioxy-4-
pregnen-3,20-dione/myoinositol and (22R)-6 α ,9 α -
20 difluoro-11 β ,21-dihydroxy-16 α ,17 α -propylmethylenedioxy-
4-pregnen-3,20-dione/lactose.
9. A process according to claim 1
c h a r a c t e r i z e d in that said substance
25 mixture is selected from formoterol fumarate
dihydrate/lactose, salbutamol sulphate/lactose and
terbutaline sulphate/lactose.
10. A process according to claim 1
30 c h a r a c t e r i z e d that step d) is carried out
at a temperature between 0 and 100°C, preferably
between 10 and 50°C and at a relative humidity so as
that the phase transition occurs, mainly above 35% RH,
preferably above 50% RH, and most preferably above 75%
35 RH.

11. A process according to claim 1
c h a r a c t e r i z e d in that the ratio between
the substances in a substance mixture is between 1:1
and 1:1000, preferably between 1:1 and 1:500, and most
5 preferred between 1:1 and 1:200 in the case where one
substance is a pharmacologically active substance and
the other one is an additive.
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Fig. 1**SUBSTITUTE SHEET**

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 94/00780

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/14, A61K 9/72, A61K 47/12, B01J 2/28
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K, B01J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, WPIL, CLAIMS, EMBASE, CHEMICAL ABSTRACT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP, A1, 0508969 (AKTIEBOLAGET ASTRA), 14 October 1992 (14.10.92) --	1-11
A	WO, A1, 9116882 (LIPOSOME TECHNOLOGY, INC.), 14 November 1991 (14.11.91) --	1-11
A	WO, A1, 8400294 (SCHRÖDER, ULF), 2 February 1984 (02.02.84) -- -----	1-11

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0508969	14/10/92	AU-A- 1534792	17/11/92
		CA-A- 2106975	12/10/92
		CZ-A- 9302116	13/04/94
		EP-A- 0580648	02/02/94
		HU-A- 65095	28/04/94
		HU-D- 9302870	00/00/00
		JP-T- 6506454	21/07/94
		WO-A- 9218110	29/10/92
WO-A1- 9116882	14/11/91	AU-A- 7908791	27/11/91
		EP-A- 0527940	24/02/93
WO-A1- 8400294	02/02/84	AU-B- 567434	19/11/87
		AU-A- 1776083	08/02/84
		DE-A- 3376797	07/07/88
		EP-A,B- 0113749	25/07/84
		US-A- 4713249	15/12/87